Synthesis of 1-(Aminomethyl)-1,2,3,4-tetrahydroisoquinolines and Their Actions at Adrenoceptors in Vivo and in Vitro

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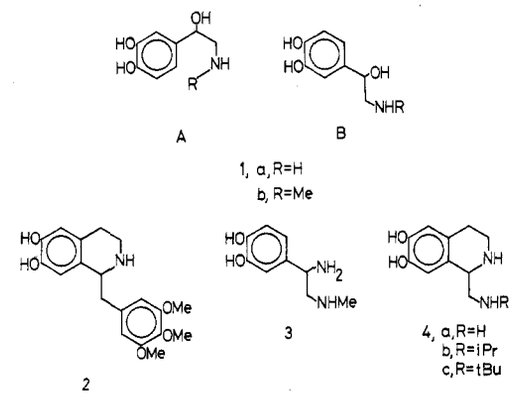
An improved synthesis of 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinolines has been developed by using aluminum hydride reduction of 1-cyano-1,2,3,4-tetrahydroisoquinolines. Three 1-(aminomethyl)-6,7-dihydroxytetrahydroisoquinolines were tested for actions at β adrenoceptors in order to examine a proposed similarity between this series and the related phenylethanolamines. The aminomethyl, (isopropylamino)methyl, and (*tert*-butylamino)methyl derivatives all showed weak partial agonist activity at β adrenoceptors and the first also showed weak α adrenoceptor agonist activity in vivo. Their low potency implies that the catechol group of THIQ sympathomimetics, such as trimetoquinol, binds differently from that of the natural catecholamines. The protonation behavior of representative aminomethyl-THIQ's was investigated by pK_a measurement and ^{1}H and ^{13}C NMR, and the compounds were shown to be substantially monoprotonated, on the exocyclic nitrogen, at physiological pH.

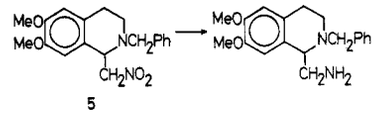
Extensive work on the structural requirements for sympathomimetic activity in phenylethanolamines related to the natural transmitters epinephrine (**1a**) and norepinephrine (**1b**) has underlined the importance of the side-chain hydroxy group for high potency.[1] The discovery of potent β-adrenoreceptor stimulant activity[2] in the benzyltetrahydroisoquinoline derivative trimetoquinol (**2**) appeared to contradict the previous conclusions, since trimetoquinol and the phenylethanolamines could be partially superimposed (A and **2**, Chart I). However, this requires the phenylethanolamine to adopt an unlikely cisoid conformation, and Brittain and co-workers made the suggestion[3] that the basic amino function of trimetoquinol might fulfill the receptor-binding role of the hydroxy group of the phenylethanolamine side chain (B and **2**, Chart I). It has been reported[4] that the diamine (**3**) retains approximately one-twentieth of the potency of epinephrine (**1b**), which offers limited support to the concept that some NH/OH functions may be interchangeable. The proposal by Brittain and co-workers also requires the 3,4,5-trimethoxy group of trimetoquinol to fulfill the role of the amino group of epinephrine, which seems somewhat less likely. If this were so, then tetrahydroisoquinolines (**4**) should be effective sympathomimetics, and a recent patent claims "muscle-relaxant" activity among derivatives in this series.[5] We set out to improve the synthesis of some appropriately substituted analogues (**4a–c**) and to examine their actions at adrenoceptors.

Chemistry. The first generally successful syntheses of the title class of compounds involved Bischler–Napieralski cyclization of *N*-phenethyl-2-phthalimidoacetamides, followed by reduction to the 1,2,3,4-tetrahydroisoquinoline and hydrazinolysis to remove the phthalyl protecting group.[6] A more attractive route (Scheme I) through the readily available 1-(nitromethyl)tetrahydroisoquinolines was reported to be unsuccessful,[7] resulting in elimination of nitromethane with a variety of reducing agents. In our hands, use of lithium aluminum hydride [or sodium bis(2-methoxyethoxy)aluminum hydride] gave yields of up to 25% of the desired product from the dimethoxy compound (**5**) (Scheme I). In seeking to improve on this, we noted that 1-cyano-2-methyl-1,2,3,4-tetrahydroisoquinoline (**6**, R = CH_3) was reported[9] to be reduced by lithium aluminum hydride to the 1-(aminomethyl)tetrahydroisoquinoline (**7**) in good yield (Scheme II). When we applied this method to the secondary amine (**6**, R = H), the cyano function was largely eliminated to give as major product

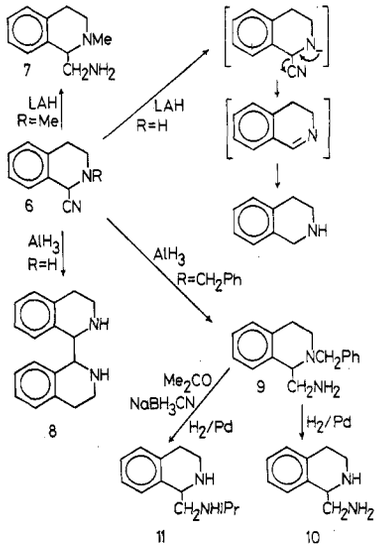
Chart I. Structural Relationships between Phenylethylamines and Tetrahydroisoquinolines



Scheme I



Scheme II



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(1) R. T. Brittain, C. M. Dean, and D. Jack, *Pharmacol. Ther., Part B*, **2**, 423 (1976), provide a useful overview.

0022-2623/83/1826-0507$01.50/0

Table I. β-Adrenoceptor Agonist Activities of THP and 4a–c in Guinea Pig, Isolated, Spontaneously Beating, Right Atrial Preparations

	intrinsic act.[a]		pD_2		drug $E_{max(50)}$/Iso[b] $E_{max(50)}$		
compd	mean	SEM	mean	SEM	mean	SEM	n
THP	0.94	0.01	6.96	0.09	26	2	4
4a	0.70	0.05	4.49	0.13	8.8×10^3	3.4×10^3	3
4b	0.42	0.03	5.05	0.09	2.7×10^3	0.4×10^3	3
4c	0.14	0.01	5.10	0.12	2.1×10^3	0.3×10^3	5

[a] Isoproterenol = 1. [b] Iso = isoproterenol.

Table II. β-Adrenoceptor Agonist Activities of THP and 4a–c in Reserpine-Pretreated, Guinea Pig, Isolated, Spontaneously Beating, Right Atrial Preparations

	intrinsic act.[a]		pD_2		drug $E_{max(50)}$/Iso[b] $E_{max(50)}$		
compd	mean	SEM	mean	SEM	mean	SEM	n
THP	0.95	0.01	7.05	0.03	38	8	4
4a	0.53	0.03	4.22	0.18	32.6×10^3	12.2×10^3	3
4b	0.59	0.06	5.18	0.06	4.4×10^3	1.3×10^3	3
4c	0.29	0.05	5.23	0.02	3.6×10^3	0.7×10^3	3

[a] Isoproterenol = 1. [b] Iso = isoproterenol.

1,2,3,4-tetrahydroisoquinoline itself, with only traces of the desired diamine. This could be attributed to initial removal of a proton from nitrogen by the basic reagent (Scheme II). However, use of the acidic reagent aluminum hydride was also unsuccessful, the major product (14%) being the unexpected 1,1′-bi(1,2,3,4-tetrahydroisoquinolinyl) (**8**). Similar products have been reported from the reduction of isoquinolines with aluminum amalgam.[24]

These problems were finally overcome by reduction of the *N*-benzyl derivative (**6**, R = CH_2Ph) with aluminum hydride, resulting in excellent yields of the aminomethyl compound (**9**), which was readily hydrogenolyzed to the model noradrenaline analogue (**10**). The model isoproterenol analogue (**11**) was prepared by reductive alkylation with acetone and sodium cyanoborohydride prior to debenzylation.

This process was applicable to the dimethoxy analogue (**12**, R = CH_3) as part of a route to the required 6,7-dihydroxy analogues (**4**, Scheme III), but a more convenient procedure was through the 6,7-bis(benzyloxy) derivatives **13** (R = CH_2Ph) and **14**, where O- and N-debenzylation could be effected simultaneously at the final stage, to give **4a**, or where intermediate alkylation was carried out, to give **4b**. The *tert*-butyl derivative **4c** was not available by this method, so a route was adopted that took advantage of the bulky *tert*-butyl group as a protecting function.

Scheme III

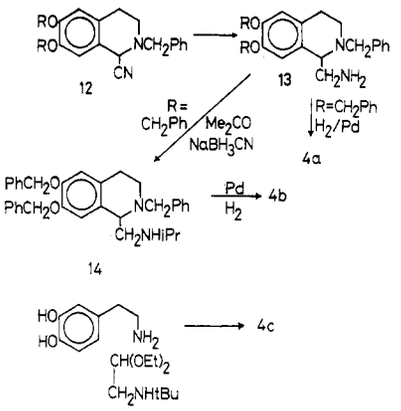


Table III. β-Adrenoceptor Antagonist Activities of 4a–c and THP in Guinea Pig, Isolated, Spontaneously Beating, Right Atrial Preparations

	pA_2		slope		
compd	mean	SEM	mean	SEM	n
4a	4.63	0.06	0.79	0.09	4
4b	4.84	0.01	0.99	0.02	5
4c	4.68	0.02	0.72[a]	0.03	6
THP	NA[b]				3

[a] Slope differs significantly from 1.0 (Student's t test, $p > 0.05$). [b] NA = no antagonism of isoproterenol responses up to 2.2×10^{-5} mol/L.

Thus, dopamine hydrochloride and (*tert*-butylamino)-acetaldehyde diethyl acetal were condensed in a Pictet–Spengler reaction to give the required product directly (Scheme III). With less bulky N-substituents, the amino group of the amino acetal would need to be protected, as in a recent report[5] where *N*-benzyloxycarbonyl functions were used.

Pharmacology. Preliminary tests showed that only the 6,7-dihydroxy analogues (**4a–c**) possessed any agonist or antagonist activity; the synthetic precursors and model compounds described in Schemes I–III were inactive. The detailed examination was therefore confined to compounds **4a–c**, and the results are summarized in Tables I–VI. Isoproterenol was used as standard throughout, but the compounds were also compared to tetrahydropapaveroline (THP) as a representative 6,7-dihydroxytetrahydroisoquinoline.

(2) E. Yamato, M. Hirakura, and S. Sugasawa, *Tetrahedron, Suppl.*, 8(1), 129 (1966). Y. Iwasawa and A. Kiyomoto, *Jpn. J. Pharmacol.*, **17**, 143 (1967). J. Houston and I. W. Rodger, *Clin. Exp. Pharmacol. Physiol.*, 1, 401 (1974). The subject has recently been reviewed: D. Beaumont and R. D. Waigh, *Prog. Med. Chem.*, **18**, 45 (1981).
(3) R. T. Brittain, D. Jack, and A. C. Ritchie, *Adv. Drug Res.*, **5**, 197 (1970).
(4) G. Lehmann and L. O. Randall, *J. Pharmacol. Exp. Ther.*, **93**, 114 (1948).
(5) T. Kishimoto, H. Kochi, and M. Kato, German Offen. 2549901 (1976). T. Kishimoto, I. Ueda, and M. Kato, British Patent 1553230 (1979).
(6) H. J. Harwood and T. B. Johnson, *J. Am. Chem. Soc.*, **55**, 4178 (1933). See also L. G. Humber, *Can. J. Chem.*, **49**, 857 (1971). G. Redeuilh, B. Marcot and C. Viel, *Bull. Soc. Chim. Fr.*, 850 (1975). Y. Takeo, *Yakugaku Zasshi*, **79**, 1003 (1959); *Chem. Abstr.*, **54**, 5679e (1960).
(7) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 1434 (1925).
(8) H. C. Brown and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1464 (1966).
(9) H. Boehme and K.-P. Stoecker, *Chem. Ber.*, **105**, 1578 (1972).

Table IV. β-Adrenoceptor Agonist Activities of 4a-c and THP in Guinea Pig, Isolated, Carbachol-Contracted Tracheal Preparations

	intrinsic act.[a]		pD_2		drug $E_{max(50)}$/Iso $E_{max(50)}$		
compd	mean	SEM	mean	SEM	mean	SEM	n
THP	0.62	0.04	6.45	0.09	6	1	4
4a	0.20[b]	0.02	3.44[b]		2.5×10^{4}[c]	0.6×10^{5}	4
4b	0.06[b]	0.02	3.49[b]		ND		3
4c	0.18[b]	0.01	3.51[b]		2.0×10^{4}[c]	0.6×10^{5}	5

[a] Isoproterenol = 1. [b] The maximum concentration used was 100 μg/mL. This did not give maximum responses. Therefore, estimates of intrinsic activities are low, the values merely reflecting the response to 100 μg/mL. Likewise, pD_2 values were not determined. Values cited here are −log (molar equivalent of 100 μg/mL). [c] Ratio determined at concentrations required to produce 15% of maximum isoproterenol response.

All four drugs (4a–c) and THP increased atrial rate, but maximum effects were less than those of isoproterenol. These effects were blocked by propranolol (1 μmol/L). Because of differences in intrinsic activity between the agents and isoproterenol, activity ratios rather than potency ratios were used in characterizing the drugs. The activity ratio is the ratio of the molar concentration of the drug required to produce 50% of its maximum effect [$E_{max(50)}$] and the molar concentration of isoproterenol required to produce its $E_{max(50)}$ in the same experiment. Intrinsic activities, pD_2 values, and activity ratios are shown in Table I. Table II shows similar results from reserpine pretreated guinea pigs.

Antagonistic Action. All drugs, with the exception of THP, shifted cumulative concentration–effect curves of isoproterenol to the right without affecting their maximum responses. Atrial rate was increased by the concentrations of the drugs required for antagonistic action; the increased rate was sustained over the 15-min contact period. pA_2 values and slopes of the relationship between log (dose ratio minus 1) and negative log (molar antagonist concentration) from all experiments are shown in Table III.

Guinea Pig Trachea. Agonistic Action. THP produced the greatest relaxing activity, and the maximum effect was obtained within the concentration range studied. The analogues 4a–c were very weak agonists, and with the highest concentration used (100 μg/mL), maximum effects were not obtained. Thus, pD_2 values, intrinsic activities, and activity ratios of the drugs could not be calculated, but approximations of the values are shown in Table IV. The agonist effects were blocked by propranolol (1 μmol/L).

Antagonistic Action. All of the compounds under test, with the exception of THP, shifted cumulative concentration–effect curves of isoproterenol to the right without affecting their maximum effects. With the lowest concentration of the drugs (4c, 31; 4b, 32; 4a, 36 μmol/L), generally no relaxation in response to the drugs per se occurred. With concentrations 3 and 10 times higher, some relaxation occurred. pA_2 values and the slopes of the relationship between log (dose ratio minus 1) and negative log (molar antagonistic concentration) are shown in Table V.

Anesthetized Cat Cardiovascular System. All three analogues (4a–c) caused tachycardia in anesthetized and bilaterally vagotomized cats, but maximum responses were less than that produced by isoproterenol. The effect was blocked by prior administration of propranolol (100 μg/kg iv). The maximum depression of pressure caused by 4b and 4c was achieved at doses that just produced a maximum increase in heart rate. Again, the maximum depression was less than that seen with isoproterenol.

In contrast to the other agents, 4a produced a pronounced pressor response; this was abolished by prior administration of phenoxybenzamine (3 mg/kg). These

Table V. β-Adrenoceptor Antagonist Activities of 4a-c and THP in Guinea Pig, Isolated, Carbachol-Contracted Tracheal Preparations

	pA_2		slope		
compd	mean	SEM	mean	SEM	n
4a	4.66	0.08	0.58[a]	0.08	4
4b	5.05	0.05	0.57[a]	0.04	4
4c	5.76	0.69	0.44[a]	0.08	6
THP	NA[b]				3

[a] Slope differs significantly from 1.0 (Student's t test, $p > 0.05$). [b] NA = no antagonism of isoproterenol responses in concentrations up to 2.2×10^{-8} mol.

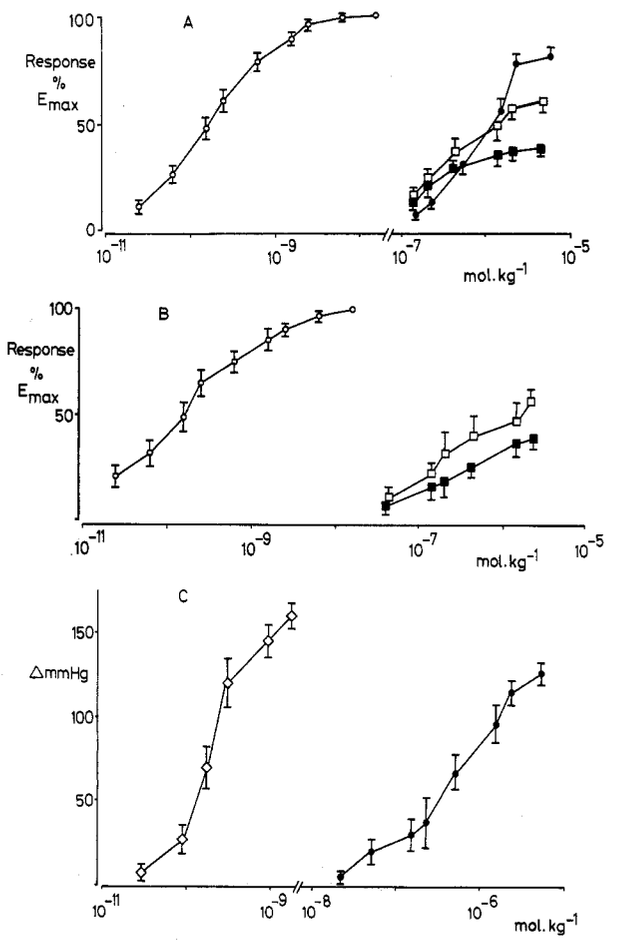


Figure 1. Log concentration–effect curves for isoproterenol (○), 4a (●), 4b (□), 4c (■), and norepinephrine (◇) in chloralose-anesthetized, bilaterally vagotomized cats: (A) positive chronotropic effect, (B) decrease in diastolic blood pressure, (C) increase in systolic blood pressure. Results in A and B are expressed in terms of percent maximum response (E_{max}) produced by isoproterenol and in C in terms of increase in pressure (mmHg). Individual points show mean plus or minus SEM responses from three to six experiments.

Table VI. Intrinsic Activity Ratios and Equieffective Dose Ratios of 4a-c in Increasing (HR) and Reducing Diastolic Blood Pressure (DBP) in Chloralose Anaesthetized, Bilaterally Vagotomized Cats

	HR				DBP				
	α[a]		activity ratio[b]		α		act. ratio		
compd	mean	SEM	mean	SEM	mean	SEM	mean	SEM	n
4a	0.80	0.06	1.27×10^4	0.42×10^4			pressor		5
4b	0.60	0.05	0.17×10^4	0.05×10^4	0.56	0.07	2.20×10^3	0.81×10^3	5
4c	0.38	0.03	0.09×10^4	0.01×10^4	0.34	0.05	1.05×10^3	0.72×10^3	5

[a] Isoproterenol = 1. [b] For calculation of the activity ratio, the molar concentration of the compound required to produce 50% of its own maximum response was divided by the molar concentration of isoproterenol required to produce 50% of isoproterenol maximum response in the same experiment.

results are illustrated in dose–response form in Figure 1A–C. Table VI shows the intrinsic activities and activity ratios of the compounds on heart rate and diastolic blood pressure.

Discussion

The results show that the compounds are weak partial agonists at β adrenoceptors. Thus, in guinea pig isolated preparations, they exerted a positive chronotropic effect on atria, and all relaxed tracheal smooth muscle; these effects were antagonized by the β-adrenoceptor antagonist propranolol. Their antagonistic action was manifested by their ability to block response to isoproterenol. The sympathomimetic effects appear to be due to a direct action at β adrenoceptors, since the positive chronotropic effect was unaffected by reserpine pretreatment.

In terms of drug–receptor interactions, the affinity of a partial agonist for receptors is related to its pA_2 or pD_2 values. For their antagonistic action on atria, data on the compounds under test conform with criteria for competitive interactions; the slopes of the plot between negative log (dose ratio minus 1) and negative log (molar antagonist concentration) do not differ significantly from unity. However, the data from the experiments on tracheae are inconsistent with competitive interactions at a single receptor site; the slopes of the plots are only around 0.5. Thus, the pA_2 values from atrial experiments provide a more appropriate measure of affinity than those obtained from experiments on tracheae. For agonistic potency, only the pD_2 values from atria could be determined, since the activity of the compounds on the tracheae was very low; at the highest concentration used, maximum relaxation was not obtained.

The affinities of the compounds did not change with increasing size of aminoalkyl loading at the 1-position but increased greatly when the substituent at the 1-position was a 3,4-dihydroxybenzyl group (i.e., THP); this is more closely related to, and can rotate as freely as, the catechol moiety of catecholamines. It is still uncertain which of the two dihydroxy groups, if either, combines with the catechol site of the physiological receptor. Yamato et al. found[2] that 1-[3,4-(ethylenedioxy)benzyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinolines possessed agonist activity considerably greater than that of 1-(3,4-dihydroxybenzyl)-6,7-(ethylenedioxy)-(1,2,3,4-tetrahydroisoquinolines and suggested that the two hydroxy groups in the 6- and 7-position were essential for the activity.

The high agonist activity of trimetoquinol (2) and the deleterious effect on potency of modifications to the 6,7-dihydroxy substitution pattern[10] emphasize the importance of the catechol groups in this position for receptor binding and suggest that the extra catechol moiety of THP is finding an alternative binding site, which is not the same as the ammonium binding site of the phenethanolamines, as evidenced by the present results.

In the present experiment, because of dose limitations the activities of the compounds could not be determined in the trachea. However, it seems that true values were higher than those shown in Table IV, since in occasional experiments when higher concentrations were used, they produced further relaxation. In contrast, the activities of all compounds were easily determined in the atria. With this limited information on tracheal activities, some inference can be made about selectivity for β adrenoceptors in this tissue and in the atria.

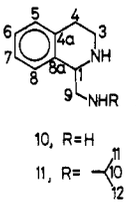
In terms of selectivity for bronchial vs. cardiac β adrenoceptors, it has been shown for phenylethanolamines that selectivity can be achieved by different means. Thus with *tert*-butyl substitution at the amino group, *N-tert*-butylnorepinephrine is found to be more selective than isoproterenol.[1]

The present results agree in some respects with the above report. With its 1-[(*tert*-butylamino)methyl] substitution, **4c** showed some degree of selectivity, in terms of a higher intrinsic activity in tracheae than in atria, although in terms of the ratio of the potency with that of isoproterenol, it is 10 times less selective for tracheal β adrenoceptors (compare ratios in Tables I and IV). It thus differs from selective β-adrenoceptor agonists, such as salbutamol, soterenol, terbutaline, and carbuterol, which show a marked selectivity for tracheal β adrenoceptors but have high intrinsic activity in atria. The question arises whether a compound with a pharmacological profile comparable to **4c** with higher intrinsic activity in tracheae than in atria and in spite of low potency vis a vis isoproterenol in tracheae could show a functional selectivity for bronchial smooth-muscle relaxation over cardiac excitation. It seems, however, that unless a molecular modification can be made to enhance their potency, such compounds are unlikely to be useful as bronchodilators in clinical practice. Indeed, the β-adrenoceptor antagonist actions of the existing compounds would presumably be clinically undesirable in asthmatics who depend on endogenous catecholamines for maintenance of adequate caliber of airways.

Results obtained with **4a–c** on blood pressure in anesthetized cats show that the in vivo β-adrenoceptor agonist activity of the compounds is enhanced by an increase in size of the 1-substituent. Thus, with its 1-(aminomethyl) substituent, **4a** possessed a strong pressor action that was prevented by the α-adrenoceptor antagonist phenoxybenzamine, but the compounds with large substituents were depressor agents, with a weak pressor action only manifested in the presence of β-adrenoceptor blockade. The enhancement in β-adrenoceptor agonist selectivity with increasing size of an N-substituent in the catecholamine molecule is well documented[1] and implies

(10) K. Ikezawa, H. Takenaga, M. Sato, H. Nakajima, and A. Kiyomoto, *Jpn. J. Pharmacol.*, **27**, 537 (1977). M. Sato, I. Yamaguchi, and A. Kiyomoto, *Jpn. J. Pharmacol.*, **17**, 153 (1967). K. Ikezawa, H. Takenaga, M. Sato, N. Itoh, H. Nakajima, and A. Kiyomoto, *Yakugaku Zasshi*, **74**, 441 (1978); *Chem. Abstr.*, **89**, 190806*a* (1978).

Table VII. ^{13}C NMR Spectral Data for 1-(Aminomethyl)-1,2,3,4-tetrahydroisoquinolines



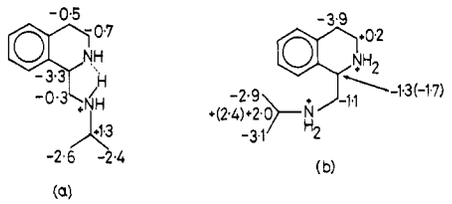
	$CDCl_3$		H_2O containing 15–20% v/v D_2O			
solvent	THIQ[d] free base	10 free base	10 free base	11 free base	11·HCl monoprotonated	11·2HCl diprotonated
C8a	134.8	137.0 (s)[a]	136.4 (s)[a]	137.3 (s)[a]	134.0 (s)[a]	128.1 (s)
C4a	136.1	136.1 (s)[a]	135.9 (s)[a]	136.5 (s)[a]	136.3 (s)[a]	133.0 (s)
C5	129.2	129.4 (d)	130.3 (d)	130.3 (d)	130.6 (d)	130.5 (d)[a]
C8	126.1	126.2 (d)[b]	127.8 (d)[b]	127.7 (d)[b]	128.4 (d)[b]	130.3 (d)[a]
C7	125.9	126.1 (d)[b]	127.3 (d)[b]	127.5 (d)[b]	127.4 (d)[b]	128.5 (d)[b]
C6	125.6	125.9 (d)[b]	127.1 (d)[b]	127.1 (d)[b]	127.4 (d)[b]	127.9 (d)[b]
C1	48.2	57.6 (d)	56.9 (d)	55.0 (d)	51.7 (d)	53.7 (d)[c]
C10				51.3 (d)	52.6 (d)	53.3 (d)[c]
C9		46.4 (t)	45.5 (t)	49.0 (t)	48.7 (t)	47.9 (t)
C3	43.8	40.3 (t)	39.9 (t)	39.5 (t)	38.8 (t)	39.7 (t)
C4	29.1	29.8 (t)	28.8 (t)	29.0 (t)	28.5 (t)	25.1 (t)
C11				22.1 (q)	19.7 (q)	19.0 (q)
C12				21.9 (q)	19.3 (q)	19.0 (q)

[a-c] Indicate assignments may be interchanged. multiplicities [singlet (s), doublet (d), triplet (t), and quartet (q)] were obtained from SFORD spectra. [d] From ref 13.

that the exocyclic amino function of **4a–c** is binding in a similar way to the amino function of phenethanolamines. If this is accepted, the low potency of **4a–c** implies that the phenethanolamine receptor does not bind readily to the 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline nucleus, at least when presented in a way that allows the exocyclic amino group to bind.

Some doubt existed concerning the protonation behavior of the diamines; we therefore sought to exclude this as a reason for lack of potency. Double protonation at physiological pH would lead to repulsion between the charged groups and the adoption of a conformation different from that suggested for active catecholamines.[11] Monoprotonation could occur on either nitrogen, with one of the alternatives bearing markedly reduced resemblance to the monobasic phenylethanolamines. Determination of pK_a values for the simple diamines (**10** and **11**) by potentiometric titration established that both would be substantially monoprotonated at physiological pH (pK_a values for **10** were 8.9 and 5.7; for **11** they were 9.2 and 5.4). Correction to 37 °C did not change this conclusion. To determine whether protonation was selective, i.e., which if either nitrogen was protonated predominantly first, we examined ^1H and ^{13}C NMR spectra of the bases **10** and **11** and the monohydrochloride and dihydrochloride of **11**. Overlapping of peaks in the ^1H NMR spectra reduced the useful information to the observation that C(1) H underwent downfield shifts of 0.18 and 1.11 ppm on mono- and diprotonation, respectively, indicating that protonation occurred preferentially on the exocyclic nitrogen. More extensive information was obtained from ^{13}C NMR spectra, although protonation shifts in ^{13}C NMR spectra of polyamines are complex.[12]

Chart II. (a) Monoprotonation and (b) Diprotonation Shifts[a] in ^{13}C NMR Spectra of 1-(Aminomethyl)-1,2,3,4-tetrahydroisoquinolines[b]



[a] In parts per million. [b] Values in parentheses are uncertain peak assignments.

^{13}C NMR chemical shifts for compounds **10** and **11** are given in Table VII. Data for compound **10** were obtained in deuteriochloroform to facilitate comparison with published assignments for 1,2,3,4-tetrahydroisoquinoline,[13] although, in fact, there were only slight differences between spectra in chloroform and water. To a certain extent the assignments are arbitrary, and with a few significant exceptions, the protonation shifts are uncertain. Fortunately, a sufficient number of the peaks can be assigned to allow useful conclusions to be drawn; the protonation shifts resulting from the assignments in the table are expressed diagrammatically (Chart II).

The salient conclusions drawn from published amine ^{13}C NMR data are that (a) β carbons invariably show upfield protonation shifts while γ and δ carbons show small upfield shifts and (b) protonation shifts for α carbons vary from 2.5 ppm upfield to 8.8 ppm downfield.[12] It is apparent that the shifts in Chart II are consistent with monoprotonation occurring substantially on the exocyclic nitrogen. Of particular significance are the shifts of the isopropyl methyl carbons, which show a substantial upfield shift on monoprotonation and a much smaller extra shift on di-

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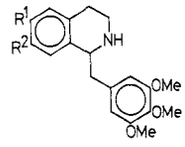
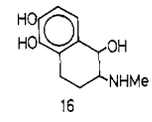
protonation, and C(4), which only shows a significant upfield shift on diprotonation. In both cases, the carbons are β to the proposed protonation site and unambiguously assignable.

Unambiguous information as to the conformation adopted by non-, mono-, and diprotonated species was not obtained. Solution of the Karplus equation for the coupling constants for C(1) H with the adjacent CH_2 group gave sets of dihedral angles from which two possible conformations for each species could be constructed. The conformations depicted in Chart II are permitted, and it is conceivable that the conformation of the monoprotonated molecule could be maintained by intramolecular hydrogen bonding. Such a conformation places the aryl and two amino functions in the same relative spatial arrangement as the aryl, amino, and hydroxy functions of arylethanolamines in what is considered to be their active conformation.[11] Further, such an arrangement closely resembles the relatively rigid and highly potent[14] tetrahydronaphthalenes, such as **16**. It appears that the diamines **4a–c** are closer in structure to active compounds in other series than is trimetoquinol. Their lack of potency compared to trimetoquinol indicated that the latter may bind to the receptor in a quite different manner from other β-adrenoceptor stimulants. For a fuller discussion, see Beaumont and Waigh.[2] The lack of potency of the two salbutamol analogues (**15a,b**) tends to support this hypothesis, although no pharmacological details were given.[15] Further work in this direction is being carried out.



15, a, R^1=OH, R^2=CH_2OH
b, R^1=CH_2OH, R^2=OH



16

Experimental Section

Chemical Methods. Melting points were obtained on a Reichert hot-plate apparatus and are corrected. Infrared spectra were obtained on a Perkin-Elmer 237 spectrophotometer from liquid films between sodium chloride plates or, for solids, from potassium chloride disks and are quoted in wavenumbers (reciprocal centimeters). Nuclear magnetic resonance spectra were obtained at 60-MHz on a Perkin-Elmer R12B instrument, at 90-MHz on a Perkin-Elmer R32 spectrometer, or at 80-MHz on a Bruker WP80 machine. The latter machine was also used to obtain ^{13}C NMR spectra at 20 MHz. Unless stated otherwise, deuteriochloroform was used as solvent with tetramethylsilane as internal standard. Chemical shifts are quoted in parts per million downfield from Me_4Si on the δ scale. Mass spectra were obtained on an AE1 MS12 spectrometer and are quoted as mass per charge ratio and relative abundance (percent) for the most abundant ions. Microanalyses was carried out on a Perkin-Elmer 240 CHN analyzer and were within 0.4% of theory. Compounds are only described as hemihydrates, where spectral data indicated a high degree of purity, and repeated recrystallization, thorough drying and repeated analyses, gave consistent results. Aluminum hydride was generated and used according to Brown and Yoon,[8] and reactions were worked up by the method of Hey and Palluel.[16]

2-Benzyl-6,7-dimethoxy-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (5). Benzyl bromide (17 mL, 142 mmol) was added to a solution of 6,7-dimethoxy-3,4-dihydroisoquinoline (13 g, 68 mmol) in dry benzene (80 mL), and the mixture was stirred and boiled under reflux for 2 h. The mixture was cooled, and the precipitate was filtered off, washed with ether, dried, and recrystallized from methanol–ether to give the *N*-benzyldihydroisoquinolinium bromide (23 g, 93%): mp 186–188 °C (from *N,N*-dimethylformamide–ethanol–ether) (lit.[17] mp 192–195 °C dec); IR 1645 cm^{-1}; ^1H NMR δ 3.0–3.4 (2 H, t, J_{app} = 8 Hz, $ArCH_2CH_2$), 3.7–4.1 (2 H, m, $CH_2CH_2N^+$), 3.84 and 3.94 (3 H, s, OCH_3), 5.47 (2 H, s, NCH_2Ph^+), 6.91 (1 H, s, ArH), 7.2–7.65 (6 H, m, ArH), 10.33 (1 H, s, C_1 H).

A solution of nitromethane (2.2 mL, 41 mmol) and potassium hydroxide (3 g, 54 mmol) in methanol (30 mL) was added to a solution of 2-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide (9.8 g, 27 mmol) in methanol (50 mL). After standing for 1 h, the mixture was evaporated to dryness, dissolved in water, neutralized with dilute hydrochloric acid, rebasified with sodium bicarbonate, and extracted with chloroform to give the **1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline** (7.8 g, 84%): ^1H NMR δ 2.1–3.4 (4 H, m, $ArCH_2CH_2N$), 3.73 (2 H, NCH_2Ph), 3.78 and 3.81 (3 H, s, OCH_3), 4.2–4.8 [3 H, m, $ArCH(N)CH_2NO_2$], 6.53 and 6.61 (1 H, s, ArH), 7.24 (5 H, s, ArH). A portion purified from acetone had mp 104–105 °C; IR 1550 and 1360 cm^{-1}. Anal. ($C_{19}H_{22}N_2O_4$) C, H, N.

Reduction of 2-Benzyl-6,7-dimethoxy-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline. 1. With Lithium Aluminum Hydride: "Normal Addition". A solution of the 1-(nitromethyl) derivative (1.9 g, 5.5 mmol) in dry tetrahydrofuran (50 mL) was added to a stirred suspension of lithium aluminum hydride (0.6 g, 16 mmol) in dry tetrahydrofuran (30 mL), and the mixture was boiled under reflux for 1 h. Workup gave a mixture of products, which were dissolved in dry ether and dripped into ethereal hydrogen chloride. The solid was collected and recrystallized from methanol to give 1-(aminomethyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (0.35 g, 16%), which was converted to the free base and gave spectral data identical with those of an authentic sample (see below).

(2) With Lithium Aluminum Hydride: "Reverse Addition". Lithium aluminum hydride (1 g, 26 mmol) was placed in a soxhlet thimble. The 1-(nitromethyl) derivative (2.8 g, 8.3 mmol) in dry tetrahydrofuran (100 mL) was placed in the flask beneath, boiled under reflux for 1 h, and worked up to give 2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (2 g, 85%): ^1H NMR δ 2.70 (4 H, br s), 3.48 and 3.60 (2 H, s), 3.70 and 3.73 (3 H, s), 6.40 and 6.53 (1 H, s), 7.1–7.5 (5 H, m). A portion crystallized from toluene–petroleum ether (bp 60–80 °C) had mp 68–69 °C (lit.[17] mp 88–89 °C). The spectral data and melting point were identical with those of an authentic sample prepared by the sodium borohydride reduction of 2-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide.

(3) With Sodium Bis(2-methoxyethoxy)aluminum Hydride. A solution of the 1-(nitromethyl) derivative (2.1 g, 6 mmol) in dry benzene (60 mL) was dripped into a stirred, boiling solution of Red-Al (6 mL), containing approximately 16 mmol of sodium bis(2-methoxyethoxy)aluminum hydride in dry benzene (40 mL), and the mixture boiled under reflux for 1 h. Dilute sodium hydroxide (40 mL) was added, and the mixture was stirred vigorously for 1 h. The organic layer was separated and evaporated to give a mixture of products, which were dissolved in ethanol and dripped into ethereal hydrogen chloride. The precipitate was collected and purified from 2-propanol to give 1-(aminomethyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride (0.6 g, 25%), which was converted to the free base and gave spectral data identical with those of an authentic sample.

1-Cyano-1,2,3,4-tetrahydroisoquinoline (6, R = H). A solution of potassium cyanide (2.5 g, 38 mmol) in water (20 mL) was added to a solution of 3,4-dihydroisoquinoline (4 g, 30 mmol) in water (20 mL) previously acidified with dilute hydrochloric acid. Extraction with ether gave the nitrile (4.7 g, 98%): IR 3340 and 2220 cm^{-1}; ^1H NMR δ 2.21 (1 H, s, exchangeable), 2.5–3.4 (4 H, m), 4.94 (1 H, s), 7.13 (4 H, s). The hydrochloride salt had mp 158–161 °C (lit.[18] mp 160–162 °C).

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Reduction of 1-Cyano-1,2,3,4-tetrahydroisoquinoline. 1. With Lithium Aluminum Hydride. 1-Cyano-1,2,3,4-tetrahydroisoquinoline (4.6 g, 29 mmol) was reduced with lithium aluminum hydride (3 g, 89 mmol) in ether to give a mixture of products. The crude products were distilled to give 1,2,3,4-tetrahydroisoquinoline (1.6 g, 41%): bp 104–106 °C (0.8 mmHg); IR 3250 cm^{-1}; ^1H NMR δ 1.42 (1 H, s), 2.5–3.2 (4 H, m), 3.85 (2 H, s), 6.7–7.3 (4 H, m). The hydrochloride salt had mp 195–196 °C (from ethanol) (lit.[19] mp 197–198 °C). The residue after distillation was dissolved in ethanol and dripped into an ethereal solution of oxalic acid. The precipitate was collected and purified from ethanol to give 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline dioxalate (0.2 g, 2%): spectral data identical with those of an authentic sample.

(2) With Aluminum Hydride. A solution of 1-cyano-1,2,3,4-tetrahydroisoquinoline (4.2 g, 27 mmol) in dry ether (50 mL) was dripped into a cooled, stirred solution of aluminum hydride (262 mmol) in dry ether (400 mL) and stirred overnight to give a mixture of products. The mixture was dissolved in ethanol and dripped into an ethereal solution of oxalic acid. The precipitate was collected and boiled in an ethanol–methanol mixture. After the mixture cooled, the precipitate was filtered off and recrystallized from water to give 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline dioxalate (0.2 g, 2%): melting point and spectral data identical with those of an authentic sample. The filtrate (ethanol–methanol) was evaporated to dryness, and the residue was recrystallized from methanol to give 1,1′-bi-(1,2,3,4-tetrahydroisoquinolyl) (8) dioxalate (0.8 g, 14%): mp 190–192 °C; ^1H NMR (D_2O; external Me_4Si) δ 2.8–3.6 (8 H, m, 2 ArCH_2CH_2NH_2^+), 4.25 (2 H, s, 2 ArCHNH_2^+), 7.1–7.5 (8 H, m, ArH); MS, m/e 133 (53), 132 (84), 104 (100). No molecular ion was observed; $C_{18}H_{20}N_2$ requires m/e 264. Anal. ($C_{22}H_{24}N_2O_8$) C, H, N. The free base gave IR 3260 cm^{-1}.

1-(Aminomethyl)-1,2,3,4-tetrahydroisoquinoline (10). Benzyl bromide (28 mL, 235 mmol) was added to a solution of 3,4-dihydroisoquinoline (18.7 g, 143 mmol) in dry ether (300 mL), and the mixture was stirred overnight at ambient temperature. The precipitate, which was hygroscopic, was filtered off to give the **dihydroisoquinolinium bromide** (31.5 g, 73%), which after drying on a rotary evaporator was obtained as a golden oil: ^1H NMR δ 3.20 (2 H, t, J_{app} = 8 Hz, ArCH_2), 4.05 (2 H, t, J_{app} = 8 Hz, $CH_2CH_2N^+$), 5.60 (2 H, s, NCH_2Ph$^+$), 7.0–8.15 (9 H, m, ArH), 10.55 (1 H, s, C_1H). A portion crystallized from aqueous ethanol–ether had mp 60–72 °C; IR 3400 (H_2O), 1655.

A solution of potassium cyanide (1 g, 15 mmol) in water (20 mL) was added to a solution of 2-benzyl-3,4-dihydroisoquinolinium bromide (3.6 g, 12 mmol) in water (20 mL) and extracted with ether to give 2-benzyl-1-cyano-1,2,3,4-tetrahydroisoquinoline (2.8 g, 96%): ^1H NMR δ 2.5–3.3 (4 H, m), 3.78 (2 H, s), 4.59 (1 H, s), 6.8–7.5 (9 H, m). A portion recrystallized from petroleum ether (bp 60–80 °C) had mp 82–84 °C (lit.[9] mp 82 °C); IR 2220 cm^{-1}. The nitrile (5.7 g, 23 mmol) dissolved in dry ether (250 mL) was added to aluminum hydride (131 mmol) in dry ether (200 mL) and stirred overnight to give 1-(aminomethyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (9; 5.1 g, 88%): IR 3360 cm^{-1}; ^1H NMR δ 1.35 (2 H, s, NH_2), 2.5–3.3 (6 H, m, ArCH_2CH_2N and CHCH_2NH_2), 3.55 [1 H, t, J = 6 Hz, ArCH(CH$_2$)N], 3.56 and 3.80 (1 H, d, J_{gem} = 13.5 Hz, CH of NCH_2Ph), 6.8–7.4 (9 H, m, ArH).

The tetrahydroisoquinoline (9; 5 g, 20 mmol) in 96% ethanol (150 mL) was hydrogenated at atmospheric pressure over 5% palladium on charcoal (1 g). Hydrogen uptake was slow, and after 24 h only 75% of theoretical uptake had occurred. The mixture was heated at 50 °C for a further 12 h. The mixture was filtered through Kieselguhr, and the filtrate was evaporated to give 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline (10; 3 g, 93%): IR 3260 cm^{-1}; ^1H NMR δ 1.91 (3 H, s, NH_2 and NH), 2.55–3.20 (6 H, m, ArCH_2CH_2NH and CHCH_2NH_2), 3.87 [1 H, t, J = 6 Hz, ArCH (CH$_2$)N], 7.05 (4 H, s, ArH). The **dioxalate salt** had mp 187–189 °C (from aqueous methanol); ^1H NMR (D_2O; DSS) δ 3.17 (2 H, m ArCH_2CH$_2$), 3.5–3.8 (4 H, m, $CH_2CH_2NH_2^+$ and CHCH_2NH_3^+), 50.1 [1 H, t, J = 6 Hz, ArCH(CH$_2$)NH_2^+], 7.32 (4 H, br s, ArH); MS, m/e 132 (100). No molecular ion was observed; $C_{10}H_{14}N_2$ requires m/e 162. Anal. ($C_{14}H_{18}N_2O_8$) C, H, N.

1-[(Isopropylamino)methyl]-1,2,3,4-tetrahydroisoquinoline (11) Dihydrochloride. 1-(Aminomethyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (9; 3.1 g, 12 mmol) in a mixture of methanol (40 mL), acetone (10 mL), and concentrated hydrochloric acid (2.4 mL, 24 mmol) was treated with sodium cyanoborohydride (1.9 g, 30 mmol), as in the preparation of **4b**, to give 2-benzyl-1-[(isopropylamino)methyl]-1,2,3,4-tetrahydroisoquinoline (3.5 g, 97%): IR 3290 cm^{-1}; ^1H NMR δ 1.00 and 1.10 [3 H, d, J = 7 Hz, CH(CH_3)$_2$], 2.4 (br, 1 H, exchangeable, NH), 2.3–3.4 (7 H, m, ArCH_2CH_2NH, CH_2NH, and CHNH), 3.55–4.0 (1 H, m, ArCHN), 3.70 (2 H, s, ArCH_2N), 6.9–7.5 (9 H, m, ArH). Of this, 3.4 g was hydrogenated over 5% palladium on charcoal (350 mg) in a mixture of 96% ethanol (80 mL) and concentrated hydrochloric acid (2.5 mL) to give, after recrystallization from ethanol, the **tetrahydroisoquinoline (11) dihydrochloride** (1.75 g, 55%): mp 230–238 °C dec; IR 3100–2300 cm^{-1}; ^1H NMR (D_2O; external Me_4Si) δ 1.37 [6 H, d, J = 7 Hz, CH(CH_3)$_2$], 2.9–3.35 (2 H, m, ArCH_2CH$_2$), 3.4–3.95 [5 H, m, $CH_2CH_2NH_2^+$ and CHCH_2NH$_2$CH(CH$_3$)$_2^+$], 5.08 [1 H, d of d, J_{AB} = 7.5 Hz, $J_{AB'}$ = 5 Hz, ArCH(CH$_2$)NH_2^+], 7.36 (4 H, s, ArH). Anal. ($C_{13}H_{22}Cl_2N_2$) C, H, N. The free base gave IR 3260 cm^{-1}; ^1H NMR δ 1.05 [6 H, d, J = 6 Hz, CH(CH_3)$_2$], 1.88 (2 H, s, exchangeable, NH and NH), 2.5–3.2 (7 H, m, ArCH_2CH_2NH, CH_2NH, and CHNH), 3.97 (1 H, d of d, J_{AB} = 8 Hz $J_{AB'}$ = 5 Hz, ArCHNH), 7.04 (4 H, s, ArH); ^1H NMR (D_2O; DSS) δ 1.07 (6 H, d, J = 7Hz), 2.5–3.2 (7 H, m), 4.02 (1 H, d of d, J_{AB} = 8 Hz, $J_{AB'}$ = 5.5 Hz), 7.16 (4 H, s), assignments as for $CDCl_3$ spectrum.

Equimolar amounts of the free base and the dihydrochloride salt were mixed together and recrystallized from ethanol-ether to give the monohydrochloride salt: mp 146–149 °C; IR 3280, 3100–2300 cm^{-1}; ^1H NMR (D_2O; external Me_4Si) δ 1.20 [6 H, d, J = 7 Hz, CH(CH_3)$_2$], 2.4–3.5 (7 H, m, ArCH_2CH_2NH, CH_2NH$_2^+$ and CHNH$_2^+$), 4.15 (1 H, d of d, J_{AB} = 8.5 Hz, $J_{AB'}$ = 5 Hz, ArCHNH), 7.05 (4 H, s, ArH). The ^{13}C NMR spectra of the free base, mono-, and dihydrochloride salts are given in Table VII.

1-(Aminomethyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (13, R = Me) Dihydrochloride Hemihydrate. A solution of potassium cyanide (2 g, 31 mmol) in water (20 mL) was added to a suspension of 2-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide (7.5 g, 21 mmol), and the mixture was extracted with ether to give 2-benzyl-1-cyano-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (6.3 g, 98%): ^1H NMR δ 2.4–3.2, (4 H, m, ArCH_2CH_2N), 3.70 and 3.74 (3 H, s, OCH$_3$), 3.72 (2 H, s, ArCH_2N) 4.54 [1 H, s, ArCHN(CN)], 6.51 and 6.53 (1 H, s, ArH), 7.1–7.5 (5 H, m, ArH). A portion recrystallized from ether–petrol (bp 60–80 °C) had mp 107–108 °C; IR 2220 cm^{-1}. A solution of the nitrile (**12**, R = Me; 4.15 g, 13.5 mmol) in a mixture of dry ether (100 mL) and dry tetrahydrofuran (5 mL) was added to a cooled, stirred solution of aluminum hydride (79 mmol) in dry ether (150 mL), and the mixture was stirred at ambient temperature for 16 h to give 1-(aminomethyl)-2-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**13**, R = Me; 3.9 g, 92%): IR 3350 cm^{-1}; ^1H NMR δ 1.7 (br, 2 H, exchangeable, NH_2), 2.3–3.3 (6 H, m, ArCH_2CH_2N and CHCH_2NH_2), 3.51 [1 H, t, J = 6 Hz, ArCH(CH$_2$)N], 3.73 (2 H, s, NCH_2Ph), 3.78 (6 H, s, 2 OCH$_3$), 6.55 (2 H, s, ArH), 7.1–7.4 (5 H, m, ArH). The **dihydrochloride hemihydrate** had mp 206–208 °C (from 2-propanol–ether). Anal. ($C_{19}H_{26}Cl_2N_2O_2 \cdot 0.5H_2O$) C, H, N.

1-(Aminoethyl)-2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (13, R = CH_2Ph) Dihydrochloride. Phosphorus pentachloride (45 g, 216 mmol) was added portionwise to a cooled, stirred solution of *N*-[2-[3,4-bis(benzyloxy)phenyl]-ethyl]formamide (31 g, 86 mmol) in dry chloroform (200 mL), and the mixture was stirred overnight at ambient temperature. Dry ether (120 mL) was added, and the precipitate was filtered off, immediately added to water (150 mL), and stirred for 24 h. The resulting fine precipitate was filtered off, resuspended in water, basified with sodium hydroxide, and extracted with ethyl acetate to give 6,7-bis(benzyloxy)-3,4-dihydroisoquinoline (19.1 g, 65%). Benzyl bromide (13.5 mL, 113 mmol) was added to a solution of the dihydroisoquinoline (19 g, 55 mmol) in dry benzene (300 mL), and the mixture was stirred at ambient temperature for 64 h. The precipitate was filtered off and washed with ether to give the crude

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product (19.7 g), which was recrystallized from ethanol–ethyl acetate–ether to give the *N*-benzyldihydroisoquinolinium bromide (16.2 g, 57%): mp 165–166 °C; IR 1640 cm^{-1}; ^1H NMR δ 3.05 (2 H, t, J_{app} = 8 Hz, $ArCH_2CH_2$), 3.80 (2 H, t, J_{app} = 8 Hz, $CH_2CH_2N^+$), 5.07 and 5.18 (2 H, s, OCH_2Ph), 5.39 (2 H, s, NCH_2Ph^+), 6.90 and 7.78 (1 H, s, Ar*H*), 7.0–7.7 (15 H, m, Ar*H*), 10.31 (1 H, s, C_1 H).

A solution of potassium cyanide (4 g, 61 mmol) in water (50 mL) was added to a solution of 2-benzyl-6,7-bis(benzyloxy)-3,4-dihydroisoquinolinium bromide (16.2 g, 31 mmol) in methanol (100 mL), methanol was then evaporated off, and the aqueous residue was extracted with ethyl acetate to give 2-benzyl-1-cyano-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (14 g, 96%): IR 2220 cm^{-1}; ^1H NMR δ 2.4–3.1 (4 H, m), 3.78 (2 H, s), 4.50 (1 H, s), 4.98 and 5.04 (2 H, s), 6.64 (2 H, s), 7.0–7.5 (15 H, m), which was dissolved in a mixture of dry ether (200 mL) and dry tetrahydrofuran (50 mL), added to aluminum hydride (153 mmol) in dry ether (250 mL), and stirred overnight to give a mixture of products. The mixture was dissolved in ethanol and dripped into ethereal hydrogen chloride, and the precipitate was collected and recrystallized from acetone to give 2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline hydrochloride (2.65 g, 18.5%): IR 2600–2200 cm^{-1}; ^1H NMR δ 2.85–3.50 (4 H, m, $ArCH_2CH_2NH^+$), 4.02 (2 H, br s, $ArCH_2NH^+$), 4.18 (2 H, s, NCH_2Ph^+), 5.00 and 5.04 (2 H, s, OCH_2Ph), 6.50 and 6.66 (1 H, s, Ar*H*), 7.1–7.7 (15 H, m, Ar*H*), 8.0–10.0 (1 H, exchangeable, NH^+). A portion recrystallized from ethanol had mp 183–186 °C. Anal. ($C_{30}H_{30}ClNO_2$) C, H, N. The free base gave δ 2.67 (4 H, br s, $ArCH_2CH_2N$), 3.46 (2 H, br s, $ArCH_2N$), 3.58 (2 H, s, NCH_2Ph), 5.00 and 5.02 (2 H, s, OCH_2Ph), 6.53 and 6.65 (1 H, s, Ar*H*), 7.1–7.7 (15 H, m, Ar*H*). The filtrate from the preceding crystallization was evaporated, and the residue was purified from 2-propanol–acetone to give 1-(aminomethyl)-2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (**13**, R = CH_2Ph) dihydrochloride (8 g, 49%): mp 177–181 °C; IR 3100–2200 cm^{-1}. Anal. ($C_{31}H_{34}Cl_2N_2O_2$) C, H, N. The free base gave IR 3350 cm^{-1}; ^1H NMR δ 1.4 (br, 2 H, exchangeable, NH_2), 2.45–3.2 (6 H, m, $ArCH_2CH_2N$ and $CHCH_2NH_2$), 3.3–3.6 [1 H, m, $ArCH(CH_2)N$], 3.70 (2 H, s, NCH_2Ph), 5.06 (4 H, s, 2 OCH_2Ph), 6.58 and 6.63 (1 H, s, Ar*H*), 7.0–7.7 (15 H, m, Ar*H*).

1-(Aminomethyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (4a) Dihydrochloride Hemihydrate. 1-(Aminomethyl)-2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (2.2 g, 5 mmol) in a mixture of methanol (150 mL) and concentrated hydrochloric acid (2 mL) was hydrogenated over 5% palladium on charcoal (0.6 g), the mixture was filtered through Kieselguhr, the filtrate was evaporated, and the residue was recrystallized from methanol–acetone–ether to give the **tetrahydroisoquinoline (4a) dihydrochloride hemihydrate** (0.93 g, 71%): mp 135–143 °C; IR 3400, 3300–2300 cm^{-1}; ^1H NMR (D_2O; DSS) δ 2.85–3.25 (2 H, m, $ArCH_2CH_2$), 3.45–3.90 (4 H, m, $CH_2CH_2NH_2^+$ and $CHCH_2NH_3^+$), 4.95 [1 H, t, J = 6 Hz, $ArCH(CH_2)NH_2^+$], 6.79 and 6.84 (1 H, s, Ar*H*). Anal. ($C_{10}H_{16}Cl_2N_2O_2 \cdot 0.5H_2O$) C, H, N.

6,7-Dihydroxy-1-[(isopropylamino)methyl]-1,2,3,4-tetrahydroisoquinoline (4b) Dihydrochloride. Sodium cyanoborohydride (0.85 g, 13.5 mmol) was added portionwise to a cooled, stirred solution of 1-(aminomethyl)-2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline (2.5 g, 5.4 mmol) in a mixture of methanol (30 mL), acetone (5 mL), and concentrated hydrochloric acid (1.1 mL, 11 mmol), and the mixture was stirred at ambient temperature for 16 h. The mixture was acidified with dilute hydrochloric acid, organic solvents were evaporated off, and the residue was basified with sodium bicarbonate and extracted with ethyl acetate to give 2-benzyl-6,7-bis(benzyloxy)-1-[(isopropylamino)methyl]-1,2,3,4-tetrahydroisoquinoline (2.5 g, 92%): IR 3275 cm^{-1}; ^1H NMR δ 0.98 and 1.03 [6 H, d, J = 7 Hz, $CH(CH_3)_2$], 2.3–3.3 (8 H, becoming 7 H with D_2O, m, $ArCH_2CH_2N$, CH_2N, and CHN), 3.4–3.8 (1 H, m, $ArCHN$), 3.69 (2 H, s, $ArCH_2N$), 5.06 (4 H, s, $ArCH_2O$), 6.63 and 6.66 (1 H, s, Ar*H*), 7.1–7.6 (15 H, m, Ar*H*). The dihydrochloride salt, which had mp 113–123 °C (from 2-propanol–ether), IR 3100–2200 cm^{-1} (2.1 g, 4 mmol), in methanol (150 mL) was hydrogenated over 5% palladium on charcoal (0.5 g), the mixture was filtered through Kieselguhr, the filtrate was evaporated to dryness, and the residue was purified from ethanol to give **tetrahydroisoquinoline (4b) dihydrochloride** (0.7 g, 64%): mp 241–243 °C dec; IR 3410, 3270, 3100–2200 cm^{-1}; ^1H NMR (D_2O, DSS) δ 1.43 [6 H, d, J = 7 Hz, $CH(CH_3)_2$], 2.85–3.25 (2 H, m, $ArCH_2CH_2$), 3.35–3.90 [5 H, m, $CH_2CH_2NH_2^+$ and $CHCH_2NH_2CH(CH_3)_2^+$], 4.75–5.15 [1 H, m, $ArCH(CH_2)NH_2^+$], 6.80 and 6.87 (1 H, s, Ar*H*); MS *m/e* 236 (M^+, 5), 177 (37), 164 (46), 163 (59), 162 (54), 149 (41), 72 (100). A portion recrystallized from aqueous methanol–ether had mp 252–254 °C dec (lit.[5] mp 268–270 °C dec). Anal. ($C_{13}H_{22}Cl_2N_2O_2$) C, H, N.

1-[(*tert*-Butylamino)methyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (4c) Dihydrochloride. A mixture of bromoacetaldehyde diethyl acetal (20.3 g, 0.103 mol), *tert*-butylamine (50 mL, 0.47 mol), and dry benzene (50 mL) was boiled under reflux for 48 h, cooled, and evaporated almost to dryness. The residue was dissolved in ether and washed with dilute sodium hydroxide, and the organic layer was evaporated to dryness. The residue was distilled (90 °C at 1.5 mmHg) to give *N*-(*tert*-butylamino)acetaldehyde diethyl acetal (15.6 g, 80%): decomposes at 160 °C at 758 mmHg; IR 3320 cm^{-1}; ^1H NMR δ 1.08 (9 H, s), 1.20 (6 H, t, J = 7 Hz), 0.9–1.4 (1 H, exchangeable), 2.66 (2 H, d, J = 6 Hz), 3.23–3.90 (4 H, m), 4.54 (1 H, t, J = 6 Hz). A mixture of the acetal (3 g, 15.9 mmol), dopamine hydrochloride (2 g, 10.6 mmol), 1-butanol (40 mL), concentrated hydrochloric acid (2.4 mL), and water (5 mL) was boiled under reflux in a nitrogen atmosphere for 4 h. The progress of the reaction was followed by TLC on silica eluting with ethyl acetate–acetic acid–water (15:15:10, v/v) and visualizing with 1% ferric chloride solution. The mixture was evaporated to dryness, the residue was dissolved in ethanol and filtered, and the filtrate was dripped into dry ether. The precipitate was collected and recrystallized from 2-propanol–acetone–isopropyl ether to give the **tetrahydroisoquinoline (4c) dihydrochloride** (1.1 g, 32%): mp 239–242 °C dec; IR 3330, 3075–2350 cm^{-1}; ^1H NMR (D_2O; DSS) δ 1.46 [9 H, s, $C(CH_3)_3$], 2.85–3.25 (2 H, m, $ArCH_2CH_2$), 3.4–3.8 (4 H, m, $CH_2CH_2NH_2^+$ and $CHCH_2NH_2^+$), 4.7–5.1 [1 H, m, $ArCH(CH_2)NH_2^+$], 6.78 and 6.85 (1 H, s, Ar*H*); MS, *m/e* 250 (M^+·, 13), 164 (68), 163 (72), 162 (70), 86 (100). Anal. ($C_{14}H_{24}Cl_2N_2O_2$) C, H, N.

pK_a Determination of 1-(Aminomethyl)- and 1-[(Isopropylamino)methyl]-1,2,3,4-tetrahydroisoquinolines. The pH of a solution of the test substance (1.5–2 mmol) in distilled water (50–100 mL) titrated with N/20 hydrochloric acid, delivered at a rate of 2.4 mL/min by a Watson–Marlow flow Inducer Type 22, was continually monitored by a Pye-Unicam 401 combined electrode linked through a Pye-Unicam PW9418 pH meter to a chart recorder. From the graph of pH vs. volume of titrant added, the pH at half neutralization was taken as a measure of pK_a. Values obtained were as follows: 1-(aminomethyl)-1,2,3,4-tetrahydroisoquinoline (**10**), 5.7 and 8.9; *N*-isopropyl analogue **11**, 5.4 and 9.2. The bases **10** and **11** were generated from their dioxalate and hydrochloride salts, respectively, immediately before use.

The experimentally determined values were obtained at 20 °C. It is probable that values at 37 °C would be about 0.3 pK_a units lower.[20] It is also probable that the introduction of 6,7-dihydroxy groups would alter the amine pK_a values slightly, since 2-phenylethylamine is reported[21] to have pK_a of 9.88 at 25 °C, whereas dopamine is reported[22] to have pK_a of 10.63 at 20 °C. These considerations do not alter the main conclusion that the diamines under consideration would be substantially monoprotonated under physiological conditions.

Pharmacological Methods. Guinea Pig, Isolated Preparations. Guinea pigs (300–400 g) of either sex were killed by cervical dislocation. Right atrial and tracheal preparations were removed and mounted in 10-mL tissue baths containing Krebs–Henseleit solution of the following composition (mmol/L): NaCl, 118; $NaHCO_3$, 24.9; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2$, 1.9; KH_2PO_4, 1.2; glucose, 11.1 at 37 °C. It was bubbled with 5% CO_2 in O_2. The bathing solution contained ethylenediaminetetraacetic acid (EDTA, 67 μmol/L) and ascorbic acid (10 μmol/L) to reduce oxidation of catecholamines. In all experiments a 30- to 60-min

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equilibration period was allowed before addition of drugs to the tissue bath. In some experiments, guinea pigs were injected intraperitoneally with reserpine (Serpasil, Ciba Chemical Co.) in a dose of 5 mg/kg. Tissues were removed for study 18–24 h later. These preparations were tested with tyramine at a concentration of 17 μmol/L before commencing further experiment.

Right Atria. A tension of 0.02 N (2 g wt) was applied to the atrium. Contractions were recorded with a Grass force-displacement transducer (FT03), and the rate was recorded with a Grass tachograph (7P44B1) on a polygraph (790).

To obtain agonist activity, two cumulative concentration–response curves to isoproterenol and a single cumulative concentration–response curve for the test compound were established with 30-min intervals. The bath was washed three times at the end of each cumulative determination. In control experiments, three successive concentration–response curves for isoproterenol were established. Slight desensitization occurred: between curves two and three the factor was 1.2. Therefore, in experiments with test compounds, only the second isoprenaline dose–response relationship was used for potency determination, and appropriate correction was made to the $E_{max(50)}$ value for the test compound.

For determination of antagonistic activity, a concentration–effect curve for isoproterenol was established before and 15 min after the drug under test was added to the tissue bath. After washing, the process was repeated with higher concentration of the drug under test. pA_2 values were determined by the method of Arunlakshana and Schild.[23]

Trachea. Tracheae were removed and placed in Krebs–Henseleit solution bubbled with CO_2 in O_2 at room temperature and then cleared of connective tissue. An incision was made longitudinally in the cartilaginous band opposite to the smooth-muscle band. Transverse cuts through approximately three-quarters of the width of the preparation at two to three ring intervals were then made alternately from each side of the trachea. A near vertical alignment of the smooth-muscle fibers along the axis through which tension was measured was thus obtained. A resting tension of 0.02 N (2 g wt) was applied to the preparation in the tissue bath, and tension was recorded as for atria.

Carbachol (10 μmol/L) was used to induce a submaximal increase in tone in the preparations. Two cumulative concentration–response curves for isoproterenol and then a single curve for the test drug were established with 30-min intervals. The bath was washed three times after each determination. Only the second curve for isoproterenol was used in potency determinations, and, as with atria, a desensitization factor (1.3) was applied to the results for the test compound. The maximum response to all drugs under test was less than that of isoproterenol, a maximum response to which was reestablished during the period of maximum response to the drug under test. pD_2 values were obtained as with atria.

Antagonistic action was established with a procedure the same as that used with atria, except that the preparations were continuously exposed to carbachol (1 μmol/L).

Anesthetized Cats. Cats of either sex and weighing 2.3–3.6 kg were anesthetized by intraperitoneal injection of a mixture of chloralose (80 mg/kg) and sodium phenobarbitone (6 mg/kg). The trachea was cannulated, but the cat was allowed to breathe spontaneously. Drugs were injected into a brachial vein. Blood pressure was recorded from a cannulated common carotid artery by using a Druck pressure transducer (PDGR75), and heart rate was recorded by using a Grass Tachograph triggered by the arterial pulse.

After constant submaximal responses to a single dose of isoproterenol, concurrent cumulative dose–response curves for effects on the heart rate and blood pressure were established. Effects of isoproterenol were first determined, followed by responses to other drugs. In each experiment, one cumulative dose–response relationship was determined. Dose–response curves were plotted in terms of percentage of the maximum responses produced by isoproterenol.

Drugs. Drugs used were isoproterenol hydrochloride (Sterling Pharmaceuticals), tetrahydropapaveroline hydrobromide (Wellcome Research Laboratories), propranolol hydrochloride (Imperial Chemical Industries), carbachol (injection BP, Abbott Laboratories), reserpine (Serpasil, Ciba-Geigy), tyramine hydrochloride (Koch-Light), α-chloralose (British Drug Houses, and pentobarbitone sodium (Nembutal sodium, Abbott Laboratories). All drugs solutions, except reserpine, carbachol, and pentobarbitone sodium, were weighed and diluted to the appropriate concentrations with Krebs–Henseleit solution for in vitro preparations or 0.9%, w/v, NaCl solution for anesthetized cat preparations at the beginning of each experiment. The commercial carbachol, reserpine, and pentobarbitone sodium preparations were used undiluted. All working solutions were kept on ice during the experimental period.

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Registry No. **4a**, 84500-62-9; **4a**·2HCl, 60085-38-3; **4b**, 84500-63-0; **4b**·2HCl, 60085-35-0; **4c**, 84500-64-1; **4c**·2HCl, 84500-65-2; **5**, 84500-66-3; **6** (R = H), 84500-67-4; **6**·HCl (R = H), 27002-40-0; **6** (R = CH_2Ph), 37039-47-7; **8** dioxolate, 84500-69-6; **9**, 40615-06-3; **10**, 84500-70-9; **10** dioxolate, 84500-71-0; **11**, 84500-72-1; **11**·HCl, 84500-73-2; **11**·2HCl, 84500-74-3; **12** (R = Me), 73154-44-6; **12** (R = CH_2Ph), 84500-75-4; **13** (R = Me), 84500-76-5; **13**·HCl (R = Me), 84500-77-6; **13** (R = CH_2Ph), 84500-78-7; **13**·HCl (R = CH_2Ph)·2HCl, 84500-79-8; **14**, 84500-80-1; **14**·2HCl, 84500-81-2; benzyl bromide, 100-39-0; 6,7-dimethoxy-3,4-dihydroisoquinoline, 3382-18-1; *N*-benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium bromide, 5096-82-2; potassium cyanide, 151-50-8; 3,4-dihydroisoquinoline, 3230-65-7; lithium aluminum hydride, 16853-85-3; sodium bis(2-methoxyethoxy)aluminum hydride, 22722-98-1; aluminum hydride, 7784-21-6; 2-benzyl-3,4-dihydroisoquinolinium bromide, 84500-82-3; acetone, 67-64-1; 2-benzyl-1-[(isopropylamino)methyl]-1,2,3,4-tetrahydroisoquinoline, 84500-83-4; *N*-[2-[3,4-bis(benzyloxy)phenyl]ethyl]formamide, 84500-84-5; 6,7-bis(benzyloxy)-3,4-dihydroisoquinoline, 84500-85-6; *N*-benzyl-6,7-bis(benzyloxy)-3,4-dihydroisoquinolinium bromide, 84500-86-7; 2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline hydrochloride, 84500-87-8; 2-benzyl-6,7-bis(benzyloxy)-1,2,3,4-tetrahydroisoquinoline, 84500-88-9; bromoacetaldehyde diethyl acetal, 2032-35-1; *tert*-butylamine, 75-64-9; *N*-(*tert*-butylamino)acetaldehyde diethyl acetal, 84500-89-0; dopamine hydrochloride, 62-31-7.

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